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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,325	08/10/2001	Martin Gleave	UBC.P-020	8469

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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
06/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/913,325	GLEAVE ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 6,8-17 and 29-39 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 6,8,10,12-17,31,32,38 and 39 is/are rejected.

7)☒ Claim(s) 9,11,29,30 and 33-37 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Claim Objections

Claims 35-37 are objected to because of the following informalities: these claims recite an antisense that is complementary to a region of the TRPM-2 mRNA that is complementary to either SEQ ID NOs: 4, 5 or 12. Since the antisense of these claims is complementary to the same portion of mRNA, it is unclear how these antisense differ from SEQ ID NOs: 4, 5 and 12. These claims appear to be duplicates of claims 9-11. Appropriate correction or clarification is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 38 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 36, 37, 39, 41 and 42 of copending Application No. 09/967,726. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to a method of treating prostate cancer by administration of a chemotherapeutic agent and an antisense oligonucleotide targeted to TRPM-2. The chemotherapeutic agent may be a taxane or mitoxanthrone. Claim 37 of the '726 application is directed to the treatment of cancers that express TRPM-2 by administering a chemotherapeutic agent and an antisense targeted to TRPM-2. Claims 37, 39, 41 and 42 of the '726 application recite specific embodiments wherein the cancers treated include prostate cancer, the antisense is one of SEQ ID NOs: 4, 5 and

12 and the chemotherapeutic agent is a taxane or mitoxanthrone. The instant claims are directed to treatment of prostate cancer with a combination of an antisense to TRPM-2 and a chemotherapeutic agent and are an obvious variation of the '726 claims because the instant claims are a species that would anticipate the generic claims of the '726 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

Claims 6, 8, 10, 12-17, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruchovsky et al. (Prostate Suppl. 1996, of record) in view of Monia et al. (US 5,563,255), Baracchini et al. (US 5,801,154), Sensibar et al. (Cancer Research 1995, of record), Kyprianou et al. (Int. J. Cancer 1997, of record) and Raghavan et al. (European Journal of Cancer 1997, of record).

The claimed invention is directed to methods of treating prostate cancer with a combination therapy comprising androgen withdrawal and an antisense oligonucleotide that inhibits expression of TRPM-2. The antisense oligonucleotide can be that designated as SEQ ID NO: 5. In additional embodiments this combination therapy is further combined with a chemotherapeutic agent such as a taxane, an antisense oligonucleotide targeted to another anti-apoptotic protein such as Bcl-2, or both.

Bruchovsky et al. teach that progression of prostate tumors to an androgen independent state can be delayed by maintaining the tumor in a state susceptible to apoptosis. Such maintenance is accomplished by repeated cycles of androgen

withdrawal and replacement. Bruchovsky et al. teach that in rats bearing a prostate tumor model such treatment resulted in an increased time period before androgen independence. These experiments demonstrated that cycles of androgen withdrawal and replacement reinduce the apoptotic potential of tumor cells. Similar treatments have been repeated in humans with prostate cancer (see figure 3 and discussion on page 16 under heading "Clinical"). Bruchovsky et al. suggest that intermittent androgen withdrawal therapy can be improved by increasing the number of cycles before androgen independence. Bruchovsky et al. further teach that the different localization of clusterin (another name for TRPM-2) in androgen-dependent and -independent tumor cells indicates deregulation of TRPM-2 expression is promoted by androgen ablation and that TRPM-2 may foster the generation of androgen-independent cells in an androgen depleted environment (see abstract and discussion on page 19 under heading "Clusterin"). On page 20 Bruchovsky et al. suggest a prostate cancer treatment that includes augmentation of intermittent therapy by administration of additional chemotherapeutic agents such as cytotoxic drugs, radiation or gene therapy. Bruchovsky et al. explicitly suggest anti-TRPM-2 or anti-Bcl-2 gene therapy in conjugation with androgen withdrawal/replacement. Bruchovsky et al. do not teach the use of anti-TRPM-2 antisense oligonucleotides as gene therapy or anti-Bcl-2 gene therapy.

It was well recognized in the art at the time of invention that antisense inhibition of gene expression is a form of gene therapy and that antisense oligonucleotides can be readily prepared to any known gene. See for example, Monia et al., who teach at column 2, lines 1-36 that teach that numerous examples are known of use of antisense

oligonucleotides as gene therapy and that it has been established by workers in the field that antisense oligonucleotides can be useful therapeutic instrumentalities and can be configured to be useful in treatment regimes for treatment of cells and animal subjects, especially humans. Monia et al. further teach at column 4, line 55 through column 8, line 60 how to target an antisense to a gene and how to modify the oligonucleotide in order to improve pharmacokinetic parameters important for therapeutic applications. Monia et al. teach in the examples the successful practice of general antisense design taught at columns 4-8 and provide a detailed blueprint for how to make and use inhibitory antisense oligonucleotides to target any known gene.

The teachings of Baracchini et al. parallel those of Monia, teaching at column 4 that oligonucleotides have recently become accepted as drugs for the treatment of disease states in animals and man. Antisense oligonucleotide therapeutic compositions capable of modulating expression of genes implicated in disease have been identified by workers in the field and efficacy has been demonstrated for several oligonucleotide drugs. Baracchini et al. further teach at columns 6-8 targeting and modification to antisense oligonucleotides.

Sensibar et al. teach phosphorothioate antisense oligonucleotides fully complementary to a nucleic acid encoding Sulfated glycoprotein-2 (an alternative name for TRPM-2), including the translation initiation codon. This sequence is identical to that designated as SEQ ID NO: 5 in the instant application. When transfected into LNCaP cells (a human prostate cancer cell line), these antisense oligonucleotides resulted in a decline of SGP-2 synthesis, indicating that expression of SGP-2 was inhibited (see

pages 2433-2435, section entitled "Effect of Antisense Oligonucleotides to SGP-2 on LNCaP Cells").

Kyprianou et al. teach that Bcl-2 expression in prostate tumors is associated with progression to androgen independence. Bcl-2 expression is also correlated with resistance to apoptosis. Kyprianou et al. suggest on page 347 that strategies that inhibit Bcl-2 such as antisense oligonucleotides may enhance prostate cancer treatment.

Raghavan et al. teach that cytotoxic chemotherapeutic agents including mitoxanthrone are commonly used in treatment of prostate cancer. Raghavan et al. further teach that taxanes such as paclitaxel have promising activity in combination therapies.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to treat prostate cancer with a combination of androgen withdrawal and antisense oligonucleotides directed to TRPM-2, including SEQ ID NO: 5. Bruchovsky et al. provide a motivation to combine androgen withdrawal with TRPM-2 gene therapy; teaching androgen withdrawal is a routine treatment for prostate cancer, showing a link between tumor progression and inappropriate TRPM-2 expression, and explicitly suggesting such combination therapies. Based on the teachings of Monia et al. and Baracchini et al., one of ordinary skill in the art would readily recognize use of antisense oligonucleotides as a route of the gene therapy suggested by Bruchovsky et al. and based on the teachings of Sensibar et al. of antisense oligonucleotides that successfully inhibit TRPM-2 expression would be motivated to use these antisense sequences. One of ordinary skill in the art would have had a reasonable expectation of

success in combining androgen withdrawal and antisense oligonucleotide gene therapy because Bruchovsky et al. teach that androgen withdrawal is a routine treatment for prostate cancer, Monia et al. and Baracchini et al. teach that antisense oligonucleotides have use as therapeutics, and Sensibar et al. teach that antisense oligonucleotides such as that designated as SEQ ID NO: 5 successfully inhibit TRPM-2 gene expression.

It would have been further obvious to modify this combination prostate cancer treatment using chemotherapeutic agents and/or antisense oligonucleotides targeted to Bcl-2. Raghavan et al. provide a motivation to use chemotherapeutic agents to treat prostate cancer, teaching that these agents are commonly used and that paclitaxel has shown promise in combination with other treatments. Kyprianou et al. provide a motivation to target Bcl-2 in prostate cancer, teaching a relationship between Bcl-2 expression and progression to androgen independence. Kyprianou et al. and Bruchovsky et al. both suggest that antisense oligonucleotides targeted to Bcl-2 may enhance other prostate cancer therapies. Additionally, Bruchovsky et al. provide a motivation to use either or both of chemotherapeutic agents and antisense oligonucleotides, suggesting a prostate cancer therapy comprising androgen withdrawal in combination with other therapeutic agents. One of ordinary skill in the art would have had a reasonable expectation of success in combining chemotherapeutic agents or Bcl-2 antisense oligonucleotide therapy with other prostate cancer therapies because Raghavan et al. teach that combination therapies comprising chemotherapeutic agents have been used for treatment of prostate cancer, Kyprianou et al. suggest that combination therapies comprising Bcl-2 inhibition would be useful and suggest use of antisense oligonucleotides to inhibit Bcl-2, and Sensibar et al. demonstrate that

antisense oligonucleotides can be used to inhibit expression of a gene associated with prostate cancer.

Thus, the invention of claims 6, 8, 10, 12-17, 31 and 32 would have been obvious, as a whole, at the time of invention.

Response to Arguments

Applicants traverse the 103 rejection by arguing there is no teaching in Sensibar of gene therapy, merely the inhibition of TRPM-2 with antisense oligonucleotides, and that an understanding in the art that the stated inhibition would be therapeutic is lacking. The rejection has been modified to include further teaching of gene therapy; it is believed this overcomes applicants' arguments.

With regard to the Sensibar paper, applicants argue the LNCaP cells are first transfected to introduce a vector that will lead to TRPM-2 (SGP-2, clusterin) expression so that the effect of suppressing this expression can be observed and the reference provides no teaching of a therapeutic use of reducing TRPM-2 expression. This characterization of the reference is not accurate. Sensibar describes separate experiments; in one LNCaP cells are treated with antisense oligonucleotides (described on page 2433) and in another (described on page 2435) the cells are treated with a vector to overexpress the protein. Nothing in the description of the antisense treatment indicates prior treatment with a TRPM-2 vector.

With regard to the expectation of success in combining the references, applicants state, "if the effect of a decrease in TRPM-2 on apoptosis was not known, then it was not known and could not be predicted that a decrease in TRPM-2 would lead to any

therapeutic benefit", and assert that the question is whether, in the absence of the knowledge of such an effect in the prior art, there can be sufficient predictability to give rise to a reasonable expectation of success. The examiner requests clarification of this statement; because the instant claims only recite that TRPM-2 expression is reduced, the relevance of whether or not the effect of TRPM-2 on apoptosis was known prior to the time of filing is not understood.

Allowable Subject Matter

Claims 9, 11, 29, 30, 33 and 34 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
June 10, 2007